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IMMUNE MEMORY

Lingering human T cells

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Immune memory relies on the generation of memory T cells that can survive long term, but the immunological requirements for their persistence in humans are unclear. In a study published in *Science Translational Medicine*, Oliveira *et al.* traced and characterized the fate of individual memory T cells following T cell infusion in patients after haploidentical haematopoietic stem cell transplantation (HSCT). The authors found that stem cell memory T (T_{SCM}) cells were the cells that, upon infusion, persisted at highest levels at long-term follow-up and antigen exposure was important in driving the expansion of these cells.

The authors have previously shown that the infusion of donor T cells expressing the herpes simplex virus thymidine kinase (TK) suicide gene and the low-affinity nerve growth factor receptor (LNGFR) surface marker after haploidentical HSCT leads to a rapid and global immune reconstitution. Now, the authors have analysed 10 long-term surviving patients treated with infusion of TK^+ T cells after T cell-depleted haploidentical HSCT. Blood samples were analyzed annually at 2 to 14 years after infusion to track clones of the infused T cells and their progeny; the TK marker enabled discrimination of infused donor cells from newly generated TK^- T cells educated in the host thymus, and the LNGFR surface marker provided the opportunity to capture these cells by flow cytometry.

At a median follow-up of 6.8 years, TK^+ T cells could be detected in all patients, and longitudinal studies performed at a yearly interval showed that long-term circulating TK^+ T cells persisted in patients at fairly constant levels. The distribution of memory subsets was similar in the batches of infused TK^+ T cells and in TK^+ T cells retrieved long term. T cell receptor sequencing indicated that polyclonal TK^+ T cells persisted for years in all memory compartments. Furthermore, they found that the extent of TK^+ T cell expansion, rather than the number of infused TK^+ T cells, was associated with the number of TK^+ T cells detected long term. Interestingly, further analysis showed that the infusion of T_{SCM} cells (defined as $CD62L^+CD45RA^+CD95^+$) was associated with TK^+ T cell expansion early after T cell transfer and with the number of TK^+ T cells circulating long term, whereas other memory T cell subsets did not significantly correlate with long-term persistence. Thus, adoptively transferred T_{SCM} cells seem to have a privileged role in T cell expansion and long-term persistence.

Memory T cells can persist for decades after primary responses, and long-term survival of memory T cells is thought to be enhanced by periodic antigen exposure. To investigate memory T cell dynamics at the antigen-specific level, the authors did longitudinal analysis of cytomegalovirus (CMV)- and influenza virus-specific TK^+ T cells. They found high numbers of antigen-specific TK^+ T cells in patients who experience CMV reactivations or clinically relevant influenza virus infections in the first months after transplant from CMV- or influenza virus-seropositive donors, and this was associated with an increased proportion of viral-specific TK^+ T cells at both early and long-term time points. Hence, antigen recognition seems to be important in driving *in vivo* expansion and persistence of TK^+ T cells.

In summary, although the patient number is low, these results indicate that treatments promoting the production of T_{SCM} cells could lead to more durable and effective treatments for T cell-based immunotherapies.

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ORIGINAL ARTICLE Oliveira, G. *et al.* Tracking genetically engineered lymphocytes long-term reveals the dynamics of T cell immunological memory. *Sci. Transl. Med.* **7**, 317ra198 (2015)